REMARKS

Applicants have amended claims 1, 10 and 19. These amendments add no new matter. Support for these amendments can be found throughout the application as filed. For example, support for "an oligonucleotide that is from about 5 to about 15 nucleotides or from about 13 to about 100 in length" can be found, at page 8, lines 23-27. Support for "statistical significance is determined using an unpaired t-test and p is less than 0.08" can be found, *inter alia,* at page 14, lines 9-10. These amendments are made without disclaimer or prejudice.

Applicants gratefully acknowledge the Examiner's statement that rejections and/or objections of record not reiterated from the previous Office Action have been withdrawn and that only rejections and/or objections presently applied are remaining.

The Office Action states that "claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 14 (sic), and 29-34 are pending in the instant application", however Applicants respectfully note that the recitation of claims 14 should actually be claim 24 and, further, that instantly pending claims 26 and 27 are missing from the list. Accordingly, the complete list of pending claims should include claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, 27, and 29-34. Appropriate confirmation by the Examiner of the pendency of claims 24, 26 and 27 is respectfully requested.

Applicants' detailed response follows. This Response and Amendment addresses the remaining bases for rejection recited in the Office Action.

Rejections under 35 U.S.C. §112, 1st (written description)

The Office Action states that claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 14 (sic), and 29-34 are pending in the instant application. In further detail, the Office Action states that the limitations "from about 5 to about 100 nucleotides in length" and "a p value of less than or equal to 0.08" have support in the application as filed. As addressed above, claims 24, 26 and 27 are pending and presumed to be included in the instant rejection.

In order to facilitate prosecution of the application, and not in acquiescence to the Examiner's rejection, Applicants have amended independent claims 1, 10 and 19. Applicants respectfully reserve the right to pursue any breadth of claim surrendered with this amendment in the future. Applicants respectfully note for the record that the instant written description rejection is improper because it is based upon amendments made by Applicants to facilitate prosecution, despite the fact that the prior rejections of record were not founded (*i.e.,* the supposed indefiniteness of the term "statistically significant" and the supposed breadth of the term "oligonucleotide" to include endogenously-synthesized antisense transcripts that are over 800 nucleotides in length). Applicants further note that the instant written description rejection is also improper because it is based upon a misapplication of the written description requirement to require a literal *ispsis verbis* basis of support (see MPEP § 2163, quoting *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991) which states that "the description need not be in *ipsis verbis* (*i.e.*, "in the same words") to be sufficient").

Nevertheless, Applicants have amended independent claims 1, 10 and 19 containing the offending clauses "from about 5 to 100 nucleotides in length" and "a p value of less than or equal to 0.08", to, respectively, "from about 5 to about 15 nucleotides or from about 13 to about 100" and "a p value of less than 0.08". Both amendments have direct, literal, *ipsis verbis* support in the application as filed, as is detailed above. These amendments obviate the instant rejection for lack of written description of these independent claims as well as corresponding dependent claims 2, 5, 6, 8, 9, 11, 14, 15, 17, 18, 20, 23, 24, 26, 27, and 29-34. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C. §112, 1st (enablement)

The Office Action states that claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 14 (sic), and 29-34 are pending in the instant application. In particular, the Office Action states that "the specification, while being enabling for a method...wherein the prodrug is administered at a dose of 50 mg/kg and the oligonucleotide is administered at a dose of 20 mg/kg" is not enabling for the full scope of the rejected claims. In further detail, the Office Action urges that the claims be

limited to coadministration of the prodrug and the oligonucleotide at the specific doses provided in the working examples. Applicants respectfully traverse for the reasons that follow.

First, it is well established that conditions present in a patent's working examples are not *per se* limiting on the invention claimed. The question then is whether one of skill in the art would require undue experimentation to determine the range of doses of the oligonucleotide and the prodrug that would provide the claimed potentiating effect. It is well established law that determining effective dose ranges is generally routine in the art and does not require undue experimentation (see, *e.g. Cross v. Iizuka*, 733 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985) where it was found that one of skill in the art could readily determine the dosage level without undue experimentation). Indeed, the practice of pharmaceutical dose determination and optimization is performed with every new drug developed, generally using both first an animal model, and then human trials. Accordingly, the practice is considered routine, not requiring of undue experimentation, and not an obstacle to enablement. This fact is apparent from an inspection of the claims of literally thousands of issued U.S. patents directed to methods of treatment with specific compositions without limitation as to the dose administered in general, or the specific doses provided in the Applicants' working examples in particular.

Second, whether the "art teaches the potentiation of antitumor activity of irinotecan by chemically modified oligonucleotides in a dose dependent manner" is not determinative of enablement of a claim that is not limited to dose. Indeed, the cited reports of an "optimal" dose do not constitute an admission that there is only one enabled embodiment. Furthermore, the several "self-admissions from the instant application" as well as the cited publications of the inventor, which the Office Action argues "indicate that the potentiation of irinotecan by antisense oligonucleotides is dependent on the dose of both agents," simply do not support a conclusion of nonenablement. Drug effects are virtually always dependent upon the dose administered, and the fact that it is true in the instant case does not support *prima facie* nonenablement.

The question is whether the application enables someone of skill in the art to make and use the invention without undue experimentation, and not whether the claim alone (in isolation of the teachings of the specification and the knowledge of skill in the art) is enabling, as the Office Action implies. The examples, which recite specific doses of drug and oligonucleotide, while supportive of the claims, are not limiting and the application provides adequate guidance to one of skill in the art to perform the claimed method to achieve a statistically significant potentiating effect. Indeed, the claim is already limited to methods using doses which achieve a statistically significant potentiating effect and so it cannot be simultaneously argued that the claim has undue breadth, since it already limited to the dose combination which provide statistically significant potentiation. To add specific dose limitations to the claim would make the existing statistically significant potentiation limitations needlessly self-limiting and outright redundant. Furthermore to require such a limitation would unfairly narrow the scope of the claims, resulting in an inequitably limited recognition of the contribution of the inventors to the field, which would allow unscrupulous infringers to readily design around the literal terms of the claim.

Accordingly, reconsideration and withdrawal of the enablement rejection is respectfully requested.

CONCLUSION

In view of the amendments to the claims and the arguments presented above, Applicants respectfully aver that the claims are in good condition for allowance, and reconsideration of the rejections and notification of such allowance is hereby respectfully requested. The time for responding to the Action has been extended to February 5, 2006 by the accompanying Petition for a One-Month Extension of Time and authorization to charge the associated fee due.

Although no other fees are believed due at this time, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. 08-0219. If the Examiner believes that a telephone conference would expedite this matter, the Examiner is respectfully requested to telephone the applicant's undersigned attorney at (617) 526-6045.

Respectfully submitted,

WILMER CUTLER PICKERING HALE AND DORR LLP

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James T. Olesen, Ph.D.
Registration No. 46, 967

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000